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PRINCIPAL INVESTIGATOR: Jackilen Shannon, Ph.D.

CONTRACTING ORGANIZATION: Oregon Health and Science University
Portland OR 97239-0396

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Jackilen Shannon, Ph.D.

E-Mail: shannoja@ohsu.edu

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INTRODUCTION

SPECIFIC AIMS:

The protocol has been modified to describe addition of a green tea and green tea plus placebo arm. Based on discussion with the Project Officer (Julie Wilberding) it was determined this change to protocol does not affect the aims supported by DOD for the fish oil only trial. Thus no changes were made to the aims, Statement of Work or primary outcomes for the DOD funded trial. The two additional green tea arms are funded through a separate source (NCCAM), thus, in the following annual report we will not discuss the green tea portion of this trial.

We are conducting a double-blind, placebo-controlled, randomized intervention study to evaluate the effects of Fish Oil (FO) supplementation use on markers of lipid metabolism in prostate tissue samples. The primary endpoints of this trial are fatty acid synthase expression, caveolin-1 expression, changes in lipid raft fractions in the plasma membrane and cell proliferation (Ki-67 expression) in benign, pre-neoplastic and neoplastic prostate tissue. The secondary endpoints include measuring the expression of SREBP-1, a transcription factor for fatty acid synthase, cell death (apoptotic fraction using TUNEL), red blood cell (RBC) fatty acid concentration and change in PSA. Subjects are men from the Portland VA Medical Center (PVAMC), the Oregon Health and Science University (OHSU) and Kaiser Permanente Northwest (KPNW) urology clinics who are scheduled for a repeat biopsy. These men will have had an initial negative biopsy yet are still considered at high risk due to continued elevated prostatic specific antigen (PSA >4μg/dl), are positive for PIN, have suspicious findings by DRE or TRUS, or other clinical finding. Approximately 5 men per month over 24 months will be recruited and randomized to receive three months of either fish oil capsules (treatment 1) or olive oil (placebo) capsules (treatment 2). Potential confounding variables are assessed through completion of a comprehensive diet history questionnaire and risk factor questionnaire, assessment of pre and post-treatment PSA and surveillance of medication and supplement use. Compliance will be assessed using pill count and evaluation of RBC fatty acid concentrations. While this study population is limited to men at high risk of disease, the results may be more broadly generalizable to any man considered at risk of prostate cancer due to standard clinical indicators such as a PSA >4μg/ml.

BODY

During FY03 this award has supported study coordination, local and federal human subjects review, subject recruitment and data collection to address our primary aims. **HUMAN SUBJECTS REVIEW:** We obtained final DOD HSSRD review and approval to add a green tea arm to the originally funded trial of FO on 2/12/07 (for OHSU and KPNW – we are still awaiting final VA IRB approval). In order to more accurately track approvals for each separate site, the DOD assigned the HSRRB Log number **A-12538.a** to PVAMC, Log number **A-12538.b** to OHSU and Log number **A-12538.c** to KPNW. With addition of the green tea arm, we have merged the site specific protocols into a single protocol. Consent forms remain site specific.

The DOD approved modifications for all three sites throughout the year. For log number A-12538.a (PVAMC), the DOD approved the addition of study personnel, the deletion of a leaving member from the study and ensured the most recent consent form incorporated these changes (DOD approval for both: 9/9/2006) and KPNW was added as a third study site (DOD approval: 3/28/2006). We have responded to the VA IRB's contingencies to add green tea to the VA study site on 3/21/2007, however, these are items which the DOD has not yet approved. For log number A-12538.b (OHSU), the

DOD approved the same staff modification referenced above (DOD approval: 11/8/2006) and approved the addition of the green tea arm to the OHSU site (DOD approval: 2/12/2007). Log number A-12538.c was added to this study in March 2006 representing KPNW as a new site. At that time, the KPNW protocol was noted as consistent with the OHSU and VA protocols (DOD approval: 3/28/2006); we met KPNW's continuing review requirements (DOD approval: 1/28/2007) and the green tea arm was added at the KPNW study site (DOD approval: 2/12/2007).

STUDY COORDINATION: Ms. Alysia Cox has joined our study staff and has stepped in to become study coordinator under the direct supervision of Ms. Farris. Ms. Cox is the primary staff responsible for patient contact and recruitment procedures as well as on-going contact with collaborating clinicians. Ms. Farris has taken on primary responsibility for human subjects' paper work, continuing review documents and maintains ongoing contact with Donna Ferrandino (CDMRC). Senior research assistant, Ms. Amy Palma, is also available and trained to make recruitment phone calls to potential subjects, conduct visits, record data and complete all paperwork on each participant. All study staff have been trained on how to collect prostate biopsy cores from subjects, which are stored in a -80°C freezer.

PROGRESS TO DATE: To date, of a total of 80 potential repeat biopsy subjects, 50 (62.5%) met our inclusion/ exclusion criteria. Of those eligible, 64% (n=32) were successfully recruited, 18 of whom have completed the trial, one participant who was administratively removed from the trial post-randomization due to non-compliance and 13 who are currently on trial.

With the addition in 2006 of OHSU and Kaiser Permanente Northwest (KPNW) as participating sites, we have combined the three site specific protocols into a single protocol allowing for ease in interpretation and implementation. As demonstrated in Table 1, the recruitment rate for the fish oil trial has been 62%. Among the men who refused to participate, 10% indicate this is due to inability to travel or pay for gas. Only one potential participant indicated that travel was a barrier after we received additional funds to allow us to reimburse men for their travel costs. Reasons for men being ineligible varied evenly between current use of statins (no longer an exclusion criterion) and use of fish oil and inability or unwillingness to stop for the duration of the trial.

Table 1. DOD RCT Recruitment History

FISH OIL TRIAL RECRUITMENT: JANUARY 2005–FEBRUARY 2007	
Fish Oil Participant Status	
Total patients eligible: 50	**N (% of all eligible)**
Enrolled in trial	31 (62.0)
Refused: gas / travel distance	5 (10.0)
Refused: other reasons	13 (26.0)
Administratively withdrawn	1 (2.0)
Total patients ineligible: 30	**N (% of all ineligible)**
Current statin use	8 (26.7)
Fish oil or Warfarin use	6 (20.0)
Other Criteria	12 (40.0)
Unknown	4 (13.3)
Total Potential Patients* : 80	

Thus, estimating that between 22 to 26% of all men with a negative biopsy undergo re-biopsy each month at each of the participating institutions, we can expect an estimated number of potential

subjects from each clinic of: KPNW, 10-15 men; PVAMC, 4 men; OHSU 3 men. Conservatively assuming a 40% response rate, we estimate successful recruitment of 6 men per month overall for a total of as many as 108 men over the next 12 months. Because of the addition of the green tea arm our recruitment just to the fish oil arms may slow somewhat. Thus we plan to continue enrollment until the end of our funding and complete any remaining laboratory and statistical analyses in the following year. To maintain adequate enrollment we have held 2 reminder/ update meetings with the Kaiser Urology staff and regularly e-mail Kaiser, VA and OHSU study clinicians about study progress and any relevant protocol modifications. Per clinician request we have recently developed an informational brochure (not approved at any site as of yet) to be provided to patients at each participating site (see attached). This will allow for patients to contact us directly. Please note, due to slow start up in year 01, we have requested an extension through February 2008. We are in continuing discussion with Shannyn Scassero. This change will assure us the time necessary to accrue an adequate number of study subjects to address the aims of this protocol.

KEY RESEARCH ACCOMPLISHMENTS: Immunohistochemistry for fatty acid synthase (FAS) and sterol regulatory element binding protein (SREBP-1) in the biopsy samples will occur in our final year of funding to allow for batching of the work and to ensure that the technicians are unaware of subject status when reviewing the samples. However, methods for quantitation of the cholesterol component of lipid rafts have been fully developed and tested in existing non-study tissue specimens.

REPORTABLE OUTCOMES: None to date

CONCLUSIONS: The primary outcome of the third year was our success in patient recruitment and the addition of a green tea and green tea plus fish oil arm to this trial. We now are recruiting from the OHSU and PVAMC urology clinics as well as two separate KPNW urology clinics. Recruitment from these additional sites not only improves our chances of reaching our accrual target, but also allows us to recruit from a more representative group of subjects. To date we have had no serious adverse events, and have only lost one individual post-randomization.

Time for a Repeat Prostate Biopsy?

You may be eligible for a research Prostate Cancer Prevention Clinical trial with Fish oil, Green Tea or placebo

Ask Dr. Mark Garzotto, Nurse Laura Peters
or contact the Study Coordinator

- Must be at least 3 months until your next prostate biopsy
- Not moving from the Portland area
- Not allergic to Fish Oil or Green Tea
- Not taking Coumadin or other blood thinners
- Not taking Fish Oil (or willing to stop for 3 months)

You may or may not personally benefit from being in this study.
However, by serving as a subject, you may help us learn how to benefit future patients

Study Coordinator
Alysia Cox 503-220-8262 x57758

Principal Investigator: Jackilen Shannon, PhD
VA Responsible Clinician: Mark Garzotto, MD

Portland Veteran Affairs Medical Center
3710 SW US Veterans Hospital Road
Mail Code: P3-HSR&D
Portland, Oregon 97239

OREGON HEALTH OHSU